Complete Summary

GUIDELINE TITLE

American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of menopause.

BIBLIOGRAPHIC SOURCE(S)

AACE Menopause Guidelines Revision Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of menopause. Endocr Pract 2006 May-Jun;12(3):315-37. [124 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: American Association of Clinical Endocrinologists. AACE medical guidelines for clinical practice for management of menopause. 1999 Nov-Dec. 12 p.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- On May 12, 2006, GlaxoSmithKline (GSK) and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of changes to the Clinical Worsening and Suicide Risk subsection of the WARNINGS section in the prescribing Information for Paxil and Paxil CR. These labeling changes relate to adult patients, particularly those who are younger adults.

  A recent meta-analysis conducted of suicidal behavior and ideation in placebo-controlled clinical trials of paroxetine in adult patients with psychiatric disorders including Major Depressive Disorder (MDD), other depression and non-depression disorders. Results of this analysis showed a higher frequency of suicidal behavior in young adults treated with paroxetine compared with placebo. Further, in the analysis of adults with MDD (all ages), the frequency of suicidal behavior was higher in patients treated with paroxetine compared with placebo. This difference was statistically significant; however, as the absolute number and incidence of events are small, these data should be interpreted with caution. All of the reported events of suicidal behavior in the adult patients with MDD were non-fatal suicide attempts, and the majority of these attempts (8 of 11) were in younger adults aged 18-30. These MDD data

suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

It is important that all patients, especially young adults and those who are improving, receive careful monitoring during paroxetine therapy regardless of the condition being treated. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Menopause

GUIDELINE CATEGORY

Risk Assessment
Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Advanced Practice Nurses
Patients
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To provide a consensus opinion about the appropriate management of menopause, with an emphasis on the hormonal therapies available to clinicians

TARGET POPULATION

Selected, symptomatic perimenopausal and early menopausal women

INTERVENTIONS AND PRACTICES CONSIDERED

Pre-Treatment

1. Individually determined benefit-versus-risk profile
2. Consideration of absolute contraindications
3. Patient education

Treatment

1. Hormonal therapy (HT)
    - Estrogen (for women who have had a hysterectomy)
    - Estrogen plus a progestational agent, administered continuously or sequentially (for women with a uterus)
2. Nonhormonal therapy
    - Lifestyle modifications
    - Prescription medications (clonidine, antidepressants, anticonvulsants [gabapentin])
    - Over-the-counter and herbal preparations (e.g., soy-based)
3. Androgen therapy (Note: The U.S. Food and Drug Administration has not yet approved any use of androgens in women. Therefore, such therapy is considered an off-label intervention at this time.)

Monitoring

1. Dual-energy x-ray absorptiometry

MAJOR OUTCOMES CONSIDERED

- Relief of menopausal symptoms
- Beneficial effects associated with interventions
- Adverse effects associated with interventions

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Evidence presented in these guidelines was obtained through MEDLINE searches and available references developed by section heads and committee members.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

1 Properly randomized controlled trial

2a Well-designed controlled trial but without randomization

2b Well-designed cohort or case-control analytic study, preferably from more than one center or research group

2c Multiple time series with or without the intervention (cross-sectional and uncontrolled investigational studies); uncontrolled experiments with dramatic results could also be regarded as this type of evidence

3 Opinions of respected authorities that are based on clinical experience; descriptive studies and case reports; reports from expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The available scientific studies cited in these guidelines have been reviewed and evaluated for strength of evidence on the basis of definitions of levels of evidence in evaluation of the published literature.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Recommendation Grades

A. Homogeneous evidence from multiple well-designed randomized controlled trials with sufficient statistical power
   Homogeneous evidence from multiple well-designed cohort controlled trials with sufficient statistical power
   ≥ 1 conclusive level 1 publications demonstrating benefit >> (outweighs) risk
B. Evidence from at least one large well-designed clinical trial, cohort or case-controlled analytic study, or meta-analysis
   No conclusive level 1 publication; ≥ 1 conclusive level 2 publications demonstrating benefit >> risk
C. Evidence based on clinical experience, descriptive studies, or expert consensus opinion
   No conclusive level 1 or 2 publication; ≥ 1 conclusive level 3 publications demonstrating benefit >> risk
   No conclusive risk at all and no conclusive benefit demonstrated by evidence
D. Not rated
   No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk
   Conclusive level 1, 2, or 3 publication demonstrating risk >> benefit

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendation grades (A-D) and levels of evidence (1-3) are defined at the end of the "Major Recommendations" field.

Note from the National Guideline Clearinghouse (NGC): The following recommendations are taken from the Executive Summary of the original guideline document.

Treatment of Symptomatic Women

In selected postmenopausal women, on the basis of an individually determined benefit-versus-risk profile, hormone therapy (HT) may be appropriate for the relief of severe menopausal symptoms (Level of Evidence [LOE] 1, grade A). Comment: Strong evidence exists that HT is the most effective intervention for menopausal hot flashes as well as vaginal and urogenital atrophic symptoms. The recommendation to use estrogen in this setting is offset by the potential risks enumerated later in the text. Careful attention should be paid to absolute

contraindications against use of estrogen (see the "Contraindications" field in this summary). The U.S. Food and Drug Administration (FDA) guidance should be followed in using HT at the lowest dose and for the shortest duration of time necessary to control such symptoms. The use of estrogen (in conjunction with a progestational agent in women with a uterus) should be thoroughly discussed by each woman with her physician.

- HT is prescribed during the perimenopause and early menopause for relief of menopausal symptoms and treatment of vulvovaginal atrophy (LOE 1, grade A).
- When used cyclically, a progestational agent should be administered in an adequate dose for 10 to 14 days each month (LOE 1, grade A).
- Amenorrhea may be achieved by using a low dose of a progestogen administered continuously (daily) in conjunction with estrogen (LOE 1, grade A).
- Long-cycle therapy with use of a progestogen for 14 days every 3 months has not been well validated for effectiveness, but it has been proposed to reduce breast exposure to progestogens (grade B).
- The dose may be reduced with advancing age (grade C).
- Estrogen in various forms may provide relief of vasomotor symptoms, and use of the transdermal or transvaginal route should be considered (LOE 1, grade B). Comment: Although it is reasonable to believe that the transdermal route of administration of estrogen avoids the hepatic first-pass effect and therefore may reduce thromboembolic risk, no randomized controlled trials (RCTs) to support this concept have been published. Likewise, local estrogen therapy may have vaginal and uterine benefits with less systemic absorption, but the same caveat applies.

Effect on Bone

- Data from multiple RCTs substantiate the efficacy of estrogens in preserving bone mass and, less consistently, preventing fractures (LOE 1). The Women's Health Initiative (WHI) was the first large clinical trial to show a significant reduction in osteoporosis-related fractures, including hip and vertebral fractures. Approximately 85% of osteoporotic fractures detected in the WHI trial were nonvertebral and nonhip fractures (LOE 1). The beneficial effects of HT on bone protection persist, even with doses of estrogen below those commonly used for relief of symptoms (LOE 2c). The decision to use estrogen for the prevention and treatment of osteoporosis should be made by the patient and her physician in the context of her age, symptoms, and other risk factors (grade B). Comment: Because other nonhormonal therapy is available for osteoporosis, use of estrogen should be considered with global risk-to benefit potential in mind.
- Each patient should be appropriately monitored with use of dual-energy x-ray absorptiometry as well as known clinical factors of fracture risk to determine the adequacy of an administered dose of estrogen (grade A).

Related Cancer

- Endometrial cancer has been shown to be increased with use of unopposed estrogen; thus, this treatment option should be avoided in women with an intact uterus (LOE 1, grade A).

- The overall hazard ratio (HR) of breast cancer in the estrogen plus progesterone (E+P) arm of the WHI trial was 1.26 (95% confidence interval [CI], 1.00 to 1.59) (LOE 1).
- In the WHI estrogen-only treatment arm, there was a lower relative risk (RR) of invasive breast cancer in the treatment group than in the placebo group (HR, 0.77; 95% CI, 0.59 to 1.01) (LOE 1).
- Comment: In the text of these guidelines, several studies (LOE 2) are cited with similar RR for breast cancer, noting that a difference may exist in the use of estrogen alone versus E+P. Therefore, the presence of a uterus and consequent need for the use of progesterone may temper the recommendation to use estrogen with regard to breast cancer risk.
- Several studies, including the E+P arm of the WHI trial, have demonstrated a decrease in colon cancer incidence (LOE 1, 2a, 2b).
- Patients may have an increase in ovarian epithelial tumors with use of estrogen for more than 10 years (LOE 2).

Vascular and Thromboembolic Disease

- Lipid profiles should be monitored to determine individual risk (LOE 1, grade A). Several progestational agents are available, which may have different biologic effects on lipid metabolism.
- In the WHI study, the incidence of venous thromboembolic disease and pulmonary embolism was 3.5 per 1,000 person-years in the E+P treatment group, in comparison with 1.7 in the placebo group (HR, 2.06). The incidence was greater with increasing age, obesity, and factor V Leiden mutations (LOE 1). Women with a history of venous thromboembolic event (VTE) should be advised about this risk when HT is being considered. Because smoking further increases risk, women should be counseled in smoking cessation (grade A).
- In both arms of the WHI trial, cerebrovascular accidents (strokes) were more common in the treated group than in the placebo group, a difference that was statistically significant at the nominal but not the adjusted levels (LOE 1).
- Observational studies such as the Nurses' Health Study have shown an RR of 0.61 for myocardial infarction (MI) in women who took estrogen early in menopause (LOE 2b), but RCTs such as Estrogen Replacement and Atherosclerosis, the Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial, and the Heart and Estrogen/Progestin Replacement Study (HERS) did not show benefit from HT in older women with preexistent coronary artery disease (CAD) (LOE 1). The E+P arm of the WHI trial showed a small increase in coronary events during the early phase of the study, whereas later the incidence was equal to that in the placebo group. The estrogen-alone group showed no significant difference from the placebo group (LOE 1). HT is not recommended for primary or secondary cardiovascular protection (grade D), although young women in the menopause transitional years with severe symptoms should not be fearful of an increase in cardiovascular risk in this setting. In fact, on the basis of published studies and ongoing investigations, estrogen therapy during early menopause may later be shown to have benefit (grade C).

Dementia

- In several meta-analyses of observational studies, the risk of dementia has been reduced with long-term use of estrogen (LOE 2), whereas in the WHI

trial, the HR for probable dementia was 2.05 (95% CI, 1.21 to 3.48) in women beyond age 65 years who were taking E+P (LOE 1). To date, use of HT for the prevention or treatment of dementia has not been recommended (grade D).

Nonhormonal Therapy

Prescription Medication

- Prescription drugs, including clonidine, antidepressants, and anticonvulsants, may have benefit for some menopausal women (on the basis of LOE 2 studies) and may be tried in individual patients who have no specific contraindications (grade B).

Over-the-Counter and Herbal Preparations

- Although they are not regulated by the FDA, supplements have the potential for interaction with other medications or medical conditions and the potential to cause harm.
- Studies have yielded inconsistent results in relief of symptoms with various preparations including black cohosh, phytoestrogens, and vitamin E (LOE 2). Women should be counseled that data regarding the estrogenic effects of soy are inconclusive. Therefore, women with a personal or strong family history of hormone-dependent cancers (breast, uterine, or ovarian), thromboembolic events, or cardiovascular events should not use soy-based therapies (grade D).

Androgen Therapy

- Normal postmenopausal women have a 50% reduction in the serum androstenedione concentration as a result of decreased adrenal production, with a consequent testosterone production from the peripheral conversion. The adrenal androgens dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) also decline with aging, independent of menopause; thus, by 40 to 50 years of age, their values are about half those for younger women (LOE 2a)
- Symptoms ascribed to androgen deficiency, such as low libido, decreased sexual response, decreased sense of well-being, poor concentration, and fatigue, may also be attributable to estrogen deficiency. Accordingly, symptoms ascribed to androgen deficiency may be a result of either androgen deficiency itself or a deficiency of estradiol (LOE 3).
- Conflicting data are available on the effects of androgen replacement therapy on sexual function in menopausal women. Administration of testosterone by various routes at supraphysiologic doses improves libido, sexual arousal, frequency of sexual fantasies, sexual function, body composition, muscle strength, and quality of life in comparison with administration of estrogen alone. Physiologic replacement testosterone therapy appears to have an inconclusive effect on sexual function (LOE 2).
- Numerous observations are compatible with androgen therapy yielding improved bone-related factors, particularly in doses that exceed the normal range (LOE 2).

- Adverse effects may occur with androgen replacement therapy at supraphysiologic levels. Acne, hirsutism, and a significant reduction in high-density lipoprotein (HDL) cholesterol levels have been described (LOE 2b).
- The FDA has not yet approved any use of androgens in women. Therefore, such therapy is considered an off-label intervention at this time (grade C).

Definitions:

Recommendation Grades

A. Homogeneous evidence from multiple well-designed randomized controlled trials with sufficient statistical power
   Homogeneous evidence from multiple well-designed cohort controlled trials with sufficient statistical power
   ≥ 1 conclusive level 1 publications demonstrating benefit >> (outweighs) risk
B. Evidence from at least one large well-designed clinical trial, cohort or case-controlled analytic study, or meta-analysis
   No conclusive level 1 publication; ≥ 1 conclusive level 2 publications demonstrating benefit >> risk
C. Evidence based on clinical experience, descriptive studies, or expert consensus opinion
   No conclusive level 1 or 2 publication; ≥ 1 conclusive level 3 publications demonstrating benefit >> risk
   No conclusive risk at all and no conclusive benefit demonstrated by evidence
D. Not rated
   No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk
   Conclusive level 1, 2, or 3 publication demonstrating risk >> benefit

Levels of Evidence

1 Properly randomized controlled trial

2a Well-designed controlled trial but without randomization

2b Well-designed cohort or case-control analytic study, preferably from more than one center or research group

2c Multiple time series with or without the intervention (cross-sectional and uncontrolled investigational studies); uncontrolled experiments with dramatic results could also be regarded as this type of evidence

3 Opinions of respected authorities that are based on clinical experience; descriptive studies and case reports; reports from expert committees

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is identified for selected recommendations (see "Major Recommendations").

Most recommendations are based on literature review. In areas of uncertainty, professional judgment was applied.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Accurate diagnosis and appropriate management of menopause in women, providing symptom relief and reduced health risks associated with long term estrogen deficiency

POTENTIAL HARMS

Hormone Therapy

- If hormone therapy (HT) is initiated after significant atherosclerotic plaque has formed, estrogen therapy may cause disruption and rupture of the plaque, leading to an acute myocardial event.
- Endometrial cancer has been shown to be increased with use of unopposed estrogen; thus, this treatment option should be avoided in women with an intact uterus.
- In the Women's Health Initiative (WHI) study, the incidence of venous thromboembolic disease and pulmonary embolism was 3.5 per 1,000 person-years in the estrogen plus progestational agent (E+P) treatment group, in comparison with 1.7 in the placebo group, with a hazard ratio (HR) of 2.06. The incidence was greater with increasing age, obesity, and factor V Leiden mutations. Women with a history of venous thromboembolic events (VTE) should be advised about this risk when HT is being considered. Because smoking further increases the risk, women should be counseled in smoking cessation.
- In summary of the information gleaned from the studies of breast cancer and HT, breast cancer risk is influenced by the duration of exposure to estrogen and progestogens. Progestogens can have an adverse influence on breast cancer detection through proliferation of estrogen-dependent mammary tissue and increasing breast density; these changes make early breast cancer detection by mammography more difficult. On the basis of epidemiologic and randomized controlled trial (RCT) evidence, there does not appear to be an increased frequency of breast cancer diagnosed through 5 to 7 years of use of HT. This translates into about 4 or fewer cases per 1,000 women after 5 years of exposure to HT, with the assumption that the controversy of the statistical significance of these studies can be validated. Of note, the increased breast cancer risk attributed to HT is less than that associated with obesity and smoking. For additional discussion about HT and breast cancer risk, see the original guideline document.

- The data suggest a possible increase in ovarian epithelial tumors with >10 years' use of estrogen only.
- In both treatment arms of the Women's Health Initiative study, cerebrovascular accidents (strokes) were more common in the treated group than in the placebo group, a difference that was statistically significant at the nominal but not at the adjusted levels. There was no increase in fatal strokes, but an increase was noted in the nonfatal category (nominal but not adjusted).
- In the Nurses' Health Study, the risk for ischemic or hemorrhagic stroke was modestly but statistically significantly increased among women taking 0.625 mg or more of conjugated equine estrogen (CEE): RR of 1.35 (95% CI, 1.08 to 1.68) for 0.625 mg/day and 1.63 (95% CI, 1.18 to 2.26) for women taking 1.25 mg/day or more.
- The side effects of progestational compounds are difficult to evaluate and will vary with the progestational agent administered. Some women experience premenstrual-tension-like symptoms, including mood swings, bloating, fluid retention, and sleep disturbance.

Nonhormonal Therapy

- Side effects of antidepressants may include nausea, dry mouth, insomnia, fatigue, sexual dysfunction, and gastrointestinal disturbances.
- Side effects, including dry mouth, postural hypotension, fatigue, and constipation, often limit the use of this clonidine.
- Side effects of gabapentin may include fatigue, dizziness, and peripheral edema.
- Because soy may have some estrogen agonist properties, long-term safety issues, especially in patients with breast cancer, remain of concern for high-dose therapy.

Androgen Therapy

- Adverse effects may occur with androgen replacement therapy at supraphysiologic levels. Acne, hirsutism, and a significant reduction in high-density lipoprotein cholesterol levels have been described.

CONTRAINDICATIONS

CONTRAINDICATIONS

The U.S. Food and Drug Administration (FDA) has recommended that hormone therapy (HT) should generally not be prescribed to women with the following conditions:

- Current, past, or suspected breast cancer
- Known or suspected estrogen-sensitive malignant conditions
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep vein thrombosis, pulmonary embolism)

- Active or recent arterial thromboembolic disease (angina, myocardial infarction [MI])
- Untreated hypertension
- Active liver disease
- Known hypersensitivity to the active substances of HT or to any of the excipients
- Porphyria cutanea tarda (absolute contraindication)

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health-care professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.
- These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

AACE Menopause Guidelines Revision Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of menopause. Endocr Pract 2006 May-Jun;12(3):315-37. [124 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Nov-Dec (revised 2006 May-Jun)

GUIDELINE DEVELOPER(S)

American Association of Clinical Endocrinologists - Medical Specialty Society

SOURCE(S) OF FUNDING

American Association of Clinical Endocrinologists (AACE)

GUIDELINE COMMITTEE

AACE Menopause Guidelines Revision Task Force

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: American Association of Clinical Endocrinologists. AACE medical guidelines for clinical practice for management of menopause. 1999 Nov-Dec. 12 p.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Clinical Endocrinologists (AACE) Web site.

Print copies: Available from the American Association of Clinical Endocrinologists (AACE), 1000 Riverside Avenue, Suite 205, Jacksonville, FL 32204

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines. Endocrine Practice; 2004 Jul-Aug;10(4):353-361

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Clinical Endocrinologists (AACE) Web site.

Print copies: Available from the American Association of Clinical Endocrinologists (AACE), 1000 Riverside Avenue, Suite 205, Jacksonville, FL 32204

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on October 28, 1999. The information was verified by the guideline developer on February 22, 2000. This NGC summary was updated by ECRI on August 10, 2006. The updated information was verified by the guideline developer on August 28, 2006.

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